Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 12, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.12.029

Transluminal Attenuation Gradient in Coronary Computed Tomography Angiography Is a Novel Noninvasive Approach to the Identification of Functionally Significant Coronary Artery Stenosis

A Comparison With Fractional Flow Reserve

Dennis T. L. Wong, MBBS (Hons),*† Brian S. Ko, MBBS (Hons),* James D. Cameron, MBBS, MD,* Nitesh Nerlekar, MBBS,* Michael C. H. Leung, MBBS (Hons), PhD,* Yuvaraj Malaiapan, MBBS,* Marcus Crossett, BA App Sc,‡ Darryl P. Leong, MBBS (Hons), MPH, PhD,† Stephen G. Worthley, MBBS, PhD,† John Troupis, MBBS,‡ Ian T. Meredith, MBBS (Hons), PhD,* Sujith K. Seneviratne, MBBS*

Adelaide and Melbourne, Australia

Objective The purpose of this study was to assess the diagnostic accuracy of TAG320 in predicting functional stenosis severity evaluated by fractional flow reserve (FFR).

Background Coronary computed tomography angiography (CCTA) has limited specificity for predicting functionally significant stenoses. Recent studies suggest that contrast gradient attenuation along an arterial lesion, or transluminal attenuation gradient (TAG), may provide assessment of functional significance of coronary stenosis. The use of 320-detector row computed tomography (CT), enabling near isophasic, single-beat imaging of the entire coronary tree, may be ideal for TAG functional assessment of a coronary arterial stenosis.

Methods We assessed the diagnostic accuracy of TAG320 using 320-row CCTA with FFR for the evaluation of functional stenosis severity in consecutive patients undergoing invasive coronary angiography and FFR for stable chest pain. The luminal radiological contrast attenuation (Hounsfield units [HU]) was measured at 5-mm intervals along the artery from ostium to a distal level where the cross-sectional area decreased to <2.0 mm^2. TAG320 was defined as the linear regression coefficient between luminal attenuation and axial distance. Functionally significant coronary stenosis was defined as $\leq$0.8 on FFR.

Results In our cohort of 54 patients (age 62.7 $\pm$ 8.7 years, 35 men, 78 vessels), TAG320 in FFR-significant vessels was significantly lower when compared with FFR nonsignificant vessels ($-$21 [$-$27; $-$16] vs. $-$11 [$-$16; $-$3] HU/10 mm, $p < 0.001$). On receiver-operating characteristic analysis, a retrospectively determined TAG320 cutoff of $-$15.1 HU/10 mm predicted FFR $\leq$0.8 with (a bootstrapped resampled) a sensitivity of 77%, specificity of 74%, positive predictive value of 67%, and negative predictive value of 86%. The combined TAG320 and CCTA assessment had an area under the curve of 0.88. There was incremental value of adding TAG320 to CCTA assessment for detection of significant FFR by Wald test ($p = 0.0001$) and integrated discrimination improvement index (0.11, $p = 0.002$).

Conclusions Assessment of TAG320 with a 320-detector row CT provides acceptable prediction of invasive FFR and may provide a noninvasive modality for detecting functionally significant coronary stenoses. Combined TAG320 and CCTA assessment may have incremental predictive value over CCTA alone for detecting functionally significant coronary arterial stenoses; however, larger studies are required to determine the benefit of combined TAG320 and CCTA assessment. (J Am Coll Cardiol 2013;61:1271–9) © 2013 by the American College of Cardiology Foundation

From the *Monash Cardiovascular Research Centre, Department of Medicine (Monash Medical Centre), Monash University and Monash Heart, Southern Health, Clayton, Australia; †Discipline of Medicine, University of Adelaide, Adelaide, Australia; and the ‡Department of Diagnostic Imaging, MMC, Southern Health, Melbourne, Australia. Dr. Wong is supported by the National Health and Medical Research Council and a National Heart Foundation Postgraduate Scholarship. Dr. Leong is supported by the National Health and Medical Research Council and a National Heart Foundation Postdoctoral Fellowship. Dr. Meredith has received honorarium from and has served as an advisor or consultant for Boston Scientific and Medtronic; and has served as a speaker or a member of the speaker's bureaus for Boston Scientific and Medtronic. Dr. Seneviratne has received honoraria for speaking at meetings sponsored by Toshiba. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 16, 2012; revised manuscript received December 16, 2012, accepted December 18, 2012.

Abbreviations and Acronyms

BMI = body mass index

CCTA = coronary computed tomography angiography

CI = confidence interval

CO = contrast opacification

FFR = fractional flow reserve

HU = Hounsfield units

IDI = integrated discrimination improvement

MDCT = multidetector computed tomography

NPV = negative predictive value

PPV = positive predictive value

QCA = quantitative coronary angiography

ROI = region of interest

TAG = transluminal attenuation gradient

Coronary computed tomography angiography (CCTA) is an accurate noninvasive method for detection and exclusion of obstructive coronary artery disease (1,2). However, CCTA has been shown to have limited specificity for predicting functionally significant stenoses (3). Although new techniques have been recently established to enhance detection for functionally significant stenoses, including the use of computed tomography (CT), fractional flow reserve (FFR), and CT stress perfusion imaging, these may require additional expertise, cost, and/or radiation exposure (4,5). Assessment of the change in intraluminal contrast attenuation across a coronary stenosis on CT may allow prediction of functionally significant stenoses with no additional radiation exposure, contrast, or complex computation technique. Recent studies have examined the kinetics of iodinated contrast media across coronary artery stenoses (6,7). Transluminal attenuation gradient (TAG), defined as the gradient of intraluminal radiological attenuation (Hounsfield units [HU]), is a novel index that has been shown to improve classification of coronary artery stenosis severity in coronary CCTA, especially in calcified lesions (6). A 320-detector row CT, enabling near isophasic, single-beat imaging of the entire coronary tree, may be ideal for TAG320 functional assessment of a coronary arterial stenosis (8). Meanwhile, another methodology called "coronary opacification" (CO) difference, defined as the HU difference across a stenosis, was demonstrated to predict abnormal (Thrombolysis In Myocardial Infarction flow grade <3) resting coronary blood flow (7). However, no study has compared these methodologies with fractional flow reserve (FFR), which is the gold standard for assessment of functional significance of coronary stenoses (9). Our primary aim was to assess the diagnostic accuracy of TAG320 and CO difference assessed by 320-detector row CT compared with invasive FFR.

See page 1280

Methods

Patients. We examined consecutive patients who underwent CCTA and FFR assessment within 2 months, between May 2009 and February 2010. Patients with more than 50% stenosis in the left main coronary artery, branch vessel disease, distal vessel disease that was <2 mm in diameter, chronic total occlusions, myocardial infarction within 3 months, history of coronary artery bypass grafting, or intractable heart failure were not included. The study was approved by the Monash Medical Centre Human Research Ethics Committee.

Invasive coronary angiography and FFR. Invasive coronary angiography was performed per standard clinical practice via a femoral or radial approach. The pressure wire (Pressure Wire 5; Radi Medical Systems, Uppsala, Sweden) was calibrated and electronically equalized with the aortic pressure before being placed distal to the stenosis in the distal third of the coronary artery being interrogated. Intracoronary glyceryl trinitrate (100 μg) was injected to minimize vasospasm. Intravenous adenosine was administered (140 μg/kg/min) via an intravenous line in the antecubital fossa. At steady-state hyperemia, FFR was assessed using the RadiAnalyser Xpress (Radi Medical Systems), calculated by dividing the mean coronary pressure measured with the pressure sensor placed distal to the stenosis by the mean aortic pressure measured through the guide catheter. FFR of ≤0.8 was taken to define ischemia in the interrogated artery and its supplied territory (10,11).

Quantitative coronary angiography. Quantitative coronary angiography (QCA) was performed on all coronary arteries of ≥1.5 mm diameter using a 19-segment coronary model (12). This was performed using a semiautomated edge detection system (Xcelera Cath R3.2, Phillips, Amsterdam, the Netherlands) by an experienced cardiologist (B.K.) who was blinded to FFR and CT findings.

CT protocol. Cardiovascular medications were ceased 48 hours before CCTA apart from beta-blockers. On arrival, an 18-gauge intravenous line was inserted in the right antecubital vein for administration of contrast. Oral and/or intravenous metoprolol was given if the resting heart rate was >65 beats/min. Patients were scanned on a 320-detector row CT scanner (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan). The scan was acquired during injection of 55 ml of 100% iohexal 56.6 g/75 ml (Omnipaque 350; GE Healthcare, Waukesha, Wisconsin) at 5 ml/s, followed by 20 ml of a 30:70 mixture of contrast and saline, followed by 30 ml of saline. Scanning was triggered in the arterial phase using automated contrast bolus tracking with the region of interest (ROI) placed in the descending aorta and automatically triggered at 300 HU. Dose-modulated retrospective electrocardiogram gating was used in the initial 5 patients of the study period. Prospective electrocardiogram gating was used in the remaining patients, covering 70% to 80% of the R–R interval.

Scanning parameters were detector collimation 320 × 0.5 mm; tube current 300 to 500 mA (depending on body mass index [BMI]); tube voltage 120 kV if the BMI is ≥25 (100 kV if BMI <25 kg/m^2); gantry rotation time 350 ms; and temporal resolution 175 ms. Prospective electrocardiogram gating was used covering 70% to 80% of the R–R interval. For images acquired at heart rates ≤65 beats/min, scanning was completed within a single R–R interval using a 180-

degree segment. In patients with a heart rate >65 beats/min, data segments from 2 consecutive beats were used for multisegment reconstruction with improved temporal resolution of 87 ms. Images were reconstructed using the filtered back-projection technique with the FCO3 algorithm.

Coronary artery analysis in CCTA. CT angiographic images were analyzed on a dedicated workstation (Vitrea FX 2.0, Vital Images, Minnetonka, Minnesota) by 2 experienced CT angiographers (M.L. and Y.M.) blinded to QCA and FFR results. The CT angiographers read independently of each other, and discrepant readings were reconciled by consensus. Image quality was determined by a 3-point scale: 1 = poor, 2 = moderate, 3 = good (M.L. and Y.M.). All segments ≥1.5 mm were analyzed using the same 19-segment coronary model for QCA (12). Each coronary segment was visually assessed for degree of luminal stenosis, and a vessel was considered significant if there was ≥1 segment that was nonevaluable or with a ≥50% luminal stenosis.

Transluminal attenuation gradient. The centerline was determined for each major coronary artery and manually corrected if necessary. Cross-sectional images perpendicular to the vessel centerline were then reconstructed. The ROI contour (size − 1 mm^2) was positioned in the center of the cross-sectional images. The position of the ROI was manually adjusted. The mean HU was measured at 5-mm intervals, from the ostium to a distal level where the cross-sectional area decreased to <2.0 mm^2. TAG320 was determined from the change in HU per 10-mm length of coronary artery and defined as the linear regression coefficient between intra-HU and length from the ostium (millimeters) (6) (Figs. 1 and 2).

The stenosis and plaque characteristics were classified in each lesion. Vessels were classified as noncalcified if the most stenotic segment was noncalcified. Vessels were classified as calcified if the most stenotic segment was calcified or partially calcified.

Contrast opacification difference. By using the same method as TAG320, the CO (maximum, mean, and minimum) differences across stenoses were calculated as the change between CO proximal to the stenosis and CO distal to the coronary stenosis:

i. CO maximum difference = pre-stenosis CO max − post-stenosis CO max
ii. CO mean difference = pre-stenosis CO mean − post-stenosis CO mean
iii. CO minimum difference = pre-stenosis CO min − post-stenosis CO min

Statistical analysis. Continuous variables are expressed as mean ± SD or median (quartiles) as appropriate, whereas categoric variables are expressed as percentage. Continuous and categoric variables were compared using the Student *t*, Mann-Whitney, or chi-square test as appropriate. Because of the repeated-measures nature of the study, a generalized estimating equation approach was used assuming a binomial probability distribution. To yield more realistic point estimates and confidence intervals (CIs) for measures of diagnostic performance, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of multidetector computed tomography (MDCT) parameters for identifying FFR ≤0.8 were bias-adjusted by bootstrap resampling with replacement 200 times from the sample and are reported with 95% CIs.

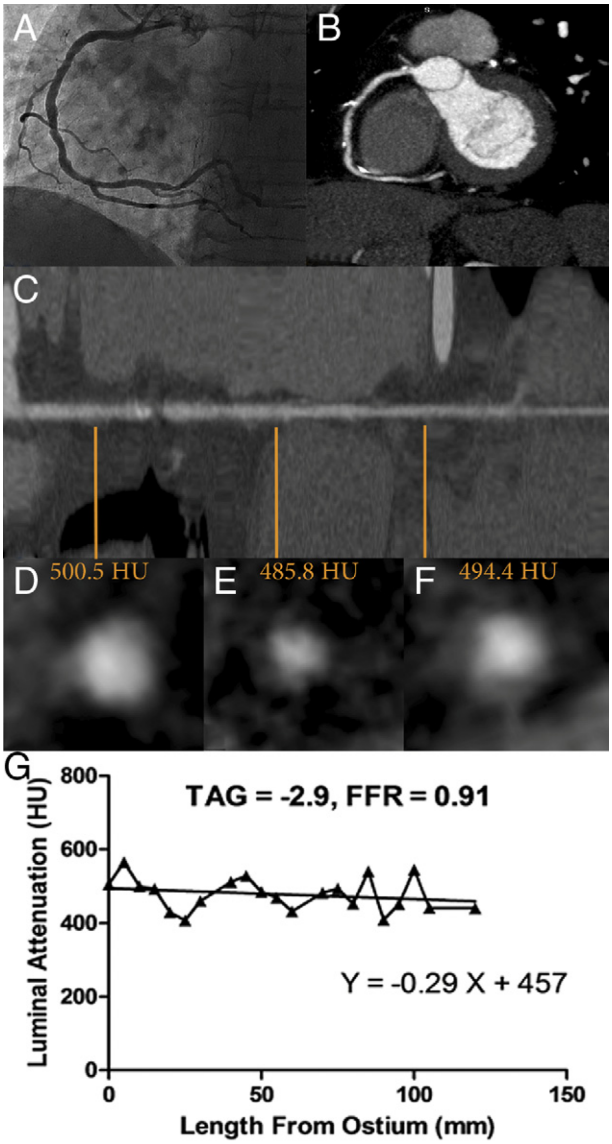

Figure 1 **Representative Example of Right Coronary Artery With Normal TAG320 and FFR Measurements**

(A) Right coronary artery with minimal obstructive plaque burden imaged by invasive coronary angiography. **(B)** Right coronary artery with minimal obstructive plaque burden imaged by CCTA. **(C to E)** Axial and representative cross-sectional views with corresponding luminal attenuation (HU) of CCTA. **(G) Black triangular dots** represent 5-mm intervals at which intraluminal attenuation (HU) was measured. TAG320 is shown. The TAG320 was −2.9, and the FFR was 0.91. FFR = fractional flow reserve; HU = Hounsfield units; TAG = transluminal attenuation gradient.

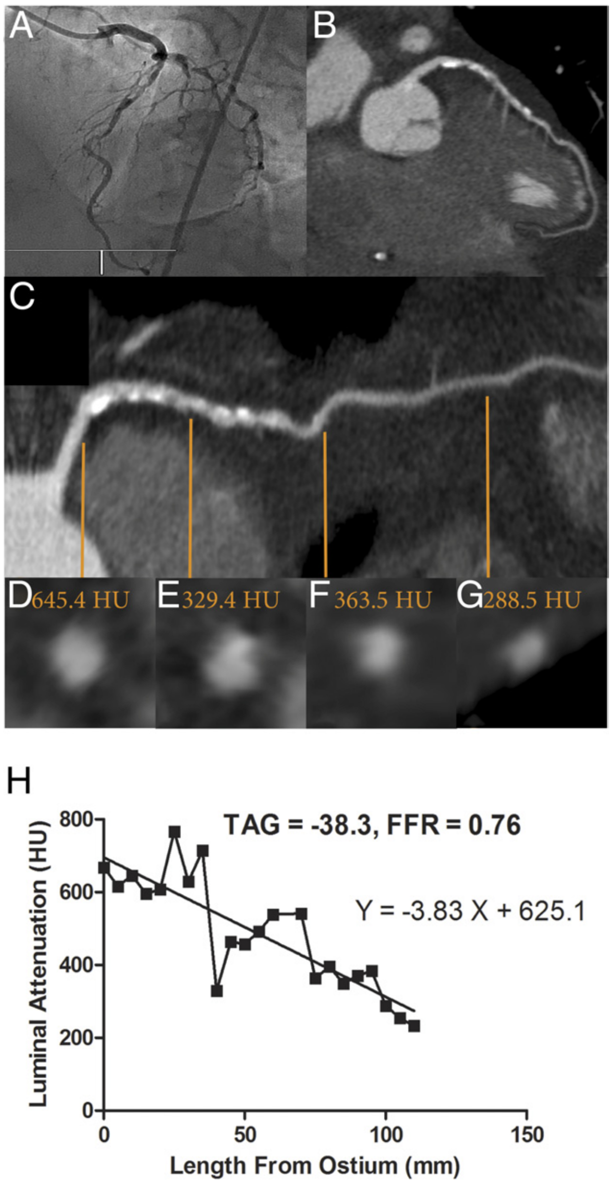

Figure 2 **Representative Example of Left Anterior Descending Artery With Abnormal TAG320 and FFR Measurements**

(A) Left anterior descending artery with significant obstructive plaque burden imaged by invasive coronary angiography. **(B)** Left anterior descending artery with significant obstructive plaque burden imaged by CCTA. **(C to G)** Axial and representative cross-sectional views with corresponding luminal attenuation (HU) of CCTA. **(H) Black triangular dots** represent 5-mm intervals at which intraluminal attenuation (HU) was measured. TAG320 is shown. The TAG320 was −38.3, and the FFR was 0.76. Abbreviations as in Figure 1.

Receiver-operating characteristic analysis was performed to identify cutoff value that maximized the sum of sensitivity and specificity of TAG320, CO (maximum, mean, minimum) differences, and CCTA in predicting FFR ≤0.8. Given the likelihood that these MDCT parameters might be interrelated, multicollinearity was assessed by the variance inflation factor (13). A variation inflation factor >10 implies significant multicollinearity.

The incremental value in adding TAG320 to CCTA in discriminating significant FFR was assessed by 2 methods. First, the incremental value of TAG320 to CCTA for predicting FFR was evaluated using the Wald test following generalized estimating equation modeling. Second, the incremental clinical utility of measuring TAG320 was assessed using the integrated discrimination improvement (IDI) index as described by Pencina et al. (14):

$$\mathrm{IDI} = (\mathrm{IS}_{new} - \mathrm{IS}_{old}) - (\mathrm{IP}_{new} - \mathrm{IP}_{old}) \text{ and}$$
$$\text{relative IDI} = (\mathrm{IS}_{new} - \mathrm{IP}_{new})/(\mathrm{IS}_{old} - \mathrm{IP}_{old})$$

where the “new” subscript refers to a model containing a novel diagnostic tool of interest in addition to conventional risk predictors, and “old” pertains to the model containing only the conventional risk markers. IS and IP are the integrals of sensitivity and (1 − specificity), respectively. In addition, the category-free net reclassification index for identification of FFR ≤0.8 using TAG320 over CCTA was calculated (14). Internal model validation was undertaken by derivation of optimism-adjusted Harrell’s c-statistic following bootstrap resampling with replacement 200 times.

Statistical analysis was performed with SPSS 18.0 (SPSS, Inc., Chicago, Illinois) and STATA 12.1 (StataCorp, College Station, Texas). A p value <0.05 was considered statistically significant.

Results

Clinical characteristics. Sixty-seven consecutive patients who underwent clinically indicated coronary angiography, FFR, and CCTA were screened. Patients with nonevaluable segments in all 3 coronary arteries due to significant artefact (n = 8) and branch or small vessel disease (n = 5) were excluded. A total of 54 patients (age 62.7 ± 8.7 years; 65% were men) formed the basis of this report. Patient characteristics are summarized in Table 1. The mean estimated radiation effective dose in our study was 5.7 mSv. This was estimated by using the scanner-reported dose-length product multiplied by a conversion factor of 0.014 (15). The CT scan parameters are summarized in Table 2.

Fractional flow reserve. FFR was performed successfully in all 54 patients, involving 78 vessels (40 left anterior descending arteries, 14 left circumflex arteries, and 24 right coronary arteries). Thirty-four patients (63%), 16 patients (30%), and 4 patients (7%) received FFR interrogation in 1-vessel territory, 2-vessel territories, and 3-vessel territories, respectively. Overall FFR reading ranged from 0.33 to 1.0 (mean, 0.80 ± 0.15). Thirty vessels (38%) were classified as functionally significant with FFR ≤0.8, whereas 48 vessels had FFR >0.8.

Accuracy of invasive QCA compared with FFR. On a per vessel basis, 28 (36%) vessels had ≥50% stenosis on QCA, whereas 11 vessels (14%) had ≥70% stenosis. When diameter stenoses on QCA ≥50% and 70% were chosen to

Table 1 Patient Characteristics (n = 54)

Age (yrs)	62.7 ± 8.7
Gender (M/F)	35/19
Diabetes	9 (17%)
Hypertension	38 (70%)
Hypercholesterolemia	38 (70%)
Current smoker	9 (17%)
Family history of IHD	27 (50%)
Previous MI	5 (9%)
Previous PCI	5 (9%)
Medications	
Aspirin	52 (96%)
Clopidogrel	27 (50%)
Beta-blocker	26 (48%)
ACEI	14 (26%)
ARB	7 (13%)
Statin	44 (81%)
Calcium channel blocker	18 (33%)

Values are mean ± SD, or n (%).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

denote significant stenoses, the bootstrapped sensitivity, specificity, PPV, and NPV were 61% (45% to 78%) and 29% (13% to 45%); 81% (69% to 93%) and 96% (90% to 100%); 68% (50% to 86%) and 82% (57% to 100%); and 76% (64% to 88%) and 67% (57% to 77%), respectively (Table 3).

Accuracy of CCTA compared with FFR. In the vessels interrogated with FFR, 45 (58%) were identified to have ≥50% on CCTA. The bootstrapped sensitivity, specificity, PPV, and NPV of CCTA for the identification of FFR significant stenoses were 94% (82% to 100%), 66% (54% to 82%), 64% (48% to 79%), and 94% (82% to 100%), respectively (Table 3).

Accuracy of TAG320 compared with FFR. Median TAG320 in FFR-significant vessels was significantly lower when compared with nonsignificant vessels (−21 [−27; −16] vs. −11 [−16; −3] HU/10 mm, $p < 0.001$). The relationship between TAG320 and FFR is presented in Figure 3. A TAG320 cutoff of −15.1 HU/10 mm predicted FFR ≤0.8 with a bootstrapped sensitivity of 77% (65% to 95%), specificity of 74% (62% to 86%), PPV of 67% (43% to 80%), and NPV of 83% (72% to 95%) (Table 3).

Impact of plaque composition on the accuracy of TAG320 compared with FFR. Of the 78 vessels, 54 were classified as calcified and 24 were classified as noncalcified. In the generalized estimating equation model, the association between CCTA and TAG320 with FFR ≤0.8 remained significant after adjustment for arterial calcification. The predictive value of TAG320 and CCTA for FFR was independent of the presence of coronary calcification when calcification was subsequently included in the model as a stand-alone covariate ($p < 0.001$ for both TAG320 and CCTA). The predictive value of TAG320 of FFR ≤0.8 was also independent of scan type (1 vs. 2 beat) on a generalized estimating equation model ($p = 0.035$).

Accuracy of contrast opacification difference compared with FFR. CONTRAST OPACIFICATION DIFFERENCES. CO MAXIMUM DIFFERENCE. The CO maximum difference in FFR-significant vessels was significantly higher when compared with nonsignificant vessels (113 [44; 171] vs. 22 [−19; 76] HU, $p = 0.001$). A CO maximum difference cutoff of 58 HU predicted FFR ≤0.8 with a bootstrapped sensitivity of 65% (47% to 82%), specificity of 68% (58% to 83%), PPV of 57% (36% to 74%), and NPV of 74% (60% to 88%) (Table 3).

CO MEAN DIFFERENCE. The CO mean difference in FFR-significant vessels was significantly higher when compared with nonsignificant vessels (113 [54; 173] vs. 18 [−14; 84] HU, $p < .001$). A retrospectively determined CO mean difference cutoff of 55 HU predicted FFR ≤0.8 with a bootstrapped sensitivity of 74% (58% to 91%), specificity of 66% (55% to 82%), PPV of 60% (39% to 74%), and NPV of 79% (62% to 92%) (Table 3).

CO MINIMUM DIFFERENCE. The CO minimum difference in FFR-significant vessels was significantly higher when compared with nonsignificant vessels (113 [45; 175] vs. 59 [2.8; 110] HU, $p = 0.011$). A retrospectively determined CO minimum difference cutoff of 49 HU predicted FFR ≤0.8 with a bootstrapped sensitivity of 77% (55% to 90%, specificity of 47% (30% to 62%), PPV of 48% (29% to 63%), and NPV of 76% (60% to 91%) (Table 3).

Comparison of TAG320, CO difference, and CCTA in predicting FFR. Multivariate generalized estimating equation analysis was undertaken to determine which if any of TAG320, CO difference, or CCTA was independently associated with FFR ≤0.8. In this analysis, CO mean was used and CO maximum and minimum were omitted for the purposes of model parsimony and because of significant

Table 2 Computed Tomography Scan Parameters

Parameter	CCTA
Heart rate (beats/min)	55.3 ± 7.1
Sinus rhythm	54 (100%)
Beta-blocker use	
Oral metoprolol	38 (70%)
Intravenous metoprolol	12 (22%)
ECG gating	
Prospective	49 (91%)
Retrospective	5 (9%)
Gantry rotation	
1	49 (91%)
2	5 (9%)
Tube volTAG320e (kV)	
100 kV	10 (19%)
120 kV	44 (81%)
Tube current (mAs)	467.3 ± 373.1
Dose length product (mGy-cm)	357.6 ± 317.2
Estimated radiation effective dose (mSv)	5.7 ± 5.2
Image quality (using subjective 3-point scale)	2.3 ± 0.7

Values are mean ± SD, or n (%).
CCTA = coronary computed tomography angiography; ECG = electrocardiogram; SD = standard deviation.

JACC Vol. 61, No. 12, 2013
March 26, 2013:1271–9

Table 3 Per Vessel Territory Diagnostic Accuracy of Coronary Computed Tomography Angiography, Transluminal Attenuation Gradient, Contrast Opacification Difference (Maximum, Mean, and Minimum), and Quantitative Coronary Angiography Compared With Fractional Flow Reserve (N = 78)

	CCTA DS ≥50%	TAG320 ≤−15.1 HU/10 mm	CO Max ≥58 HU	CO Mean ≥55 HU	CO Min ≥49 HU	QCA DS ≥50%	QCA DS ≥70%
Sensitivity (%)	94 (82–100)	77 (65–95)	65 (47–82)	74 (58–91)	77 (55–90)	61 (45–78)	68 (50–86)
Specificity (%)	66 (54–82)	74 (62–86)	68 (58–83)	66 (55–82)	47 (30–62)	29 (13–45)	82 (57–100)
PPV (%)	64 (48–79)	67 (43–80)	57 (36–74)	60 (39–74)	48 (29–63)	81 (69–93)	76 (64–88)
NPV (%)	94 (82–100)	83 (72–95)	74 (60–88)	79 (62–92)	76 (60–91)	96 (90–100)	67 (57–77)

CCTA = coronary computed tomography angiography; CO = coronary opacification; DS = diameter stenosis; HU = Hounsfield units; NPV = negative predictive value; PPV = positive predictive value; QCA = quantitative coronary angiography; TAG = transluminal attenuation gradient.

multicollinearity among the 3 CO variables (variance inflation factor 10.5). This regression identified TAG320 (coefficient −0.099, 95% CI: −0.17 to −0.027, p = 0.07) and CCTA (coefficient 2.9, 95% CI: 1.3 to 4.5, p < 0.001) as independently predictive of FFR, whereas CO mean difference was not (coefficient 0.00581, 95% CI: −0.0017 to 0.013, p = 0.128). This finding implies that most of the observed variation in FFR is related to the presence of CCTA stenosis and TAG320. The nonsignificance of CO difference if TAG320 is measured may reflect the fact that TAG320 represents a more refined index of a similar imaging signal for functional coronary stenosis significance.

Incremental value of adding TAG320 to CCTA in discriminating significant FFR. There was convincing evidence of the incremental value of adding TAG320 to CCTA assessment for detection of significant FFR by the Wald test (p = 0.0001). This is further supported by the IDI index. The IDI for the addition of TAG320 to CCTA for detection of significant FFR was 0.11 (p = 0.002). The relative IDI was 31%, and the category-free net reclassification index was 0.65 (p = 0.005). We undertook further analysis to investigate whether the improved discriminatory ability of TAG320 was related to improvement in sensitivity or specificity by examining the constituent parts of the IDI index. The measurement of TAG320 in addition to CCTA resulted in ($IS_{new} - IS_{old}$) of 0.076 (95% CI: 0.018 to 0.13) and ($IP_{new} - IP_{old}$) of −0.048 (95% CI: −0.094 to −0.001), indicating that TAG320 assessment significantly improves both sensitivity and specificity to detect clinically relevant reduction in FFR.

The optimism-adjusted Harrell's c-statistic for TAG320 in addition to CCTA for the prediction of FFR ≤0.8 was 0.88 (95% CI: 0.81 to 0.96, p < 0.001). Post-estimation testing indicated that TAG320 in addition to CCTA contributed incremental predictive value to CCTA alone (coefficient 0.086, 95% CI: 0.0046 to 0.17, p = 0.04).

Interobserver variability for TAG320 analysis. The interobserver variability for TAG320 analysis was highly reproducible between observers in 10 randomly selected vessels. The intraclass correlation coefficient was 0.9 (p < 0.001).

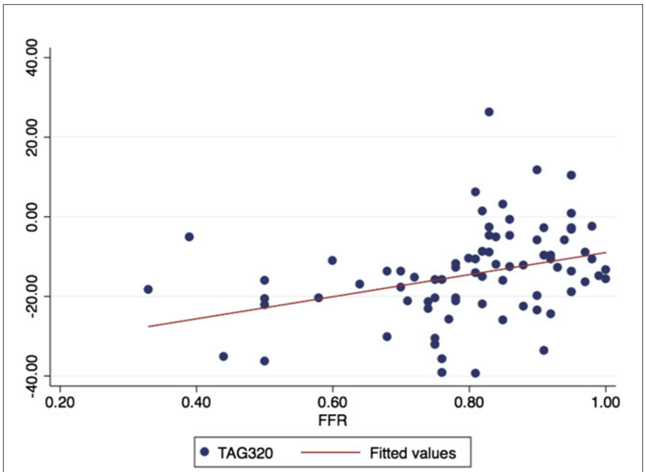

Figure 3 Scatter Plot Showing the Relationship Between TAG320 and FFR

The correlation coefficient between TAG320 and FFR was 0.43 (p < 0.001). FFR = fractional flow reserve; TAG = transluminal attenuation gradient.

Discussion

The current study has demonstrated for the first time the diagnostic accuracy of TAG320 and CO differences on a 320-detector row CT compared with an invasive functional standard: FFR. We have also illustrated the incremental value of adding TAG320 to CCTA in discriminating functionally significant coronary arterial stenoses.

The prognostic value of functional coronary lesion severity assessed by invasive FFR over anatomic evaluation by coronary angiography has been demonstrated in the FAME (Fractional Flow Reserve [FFR] versus Angiography in Multivessel Evaluation) study (11). However given the invasive nature of FFR, a noninvasive approach has gained momentum. Previous studies have assessed combined CCTA and CT perfusion as a method to provide both anatomic and functional assessment of coronary stenoses (4,16). Nonetheless, this assessment requires 2 separate (stress and rest) scans that require additional radiation exposure and contrast. More recently, computation of FFR from CCTA (CT-FFR) was described in the DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study (5). Although the study result has been encouraging, this technique requires approximately 5 hours of analysis on a parallel supercomputer. In addition, not all patients with angina could be assessed by this technique. This study excluded patients with rest angina because one of the key principles of CT-FFR is that coronary supply meets myocardial demand at rest. Similar to CT-FFR, TAG can be applied in any resting CCTA study. It does not require any modification of CCTA protocol, has no exclusion criteria for patients with rest angina, and has relatively simple analysis without the need of a parallel supercomputer, representing an extension to the possibility of noninvasive functional assessment of coronary stenoses.

TAG320, CO differences, and CCTA assessment on 320-detector row CT. The assessment of contrast opacification gradient on a 320-detector row CT has been demonstrated (8). This is the first study to report assessment of TAG320 and CO differences on 320-detector row CT. Previous TAG (6) and CO difference (7) studies have been reported using 64-slice MDCT, which is limited by its inherent longitudinal axis coverage of 4 cm. The use of a 320-detector row scanner allows the longitudinal axis to increase from 4 to 16 cm, which in most instances enabled the entire heart volume to be imaged in a single gantry rotation and a breath-hold time of 1 to 2 s. TAG and CO differences depend on the luminal attenuation values, the time-density curve of the intravascular contrast agent, and the scanning time. Therefore, 320-detector row CT, enabling near isophasic, single-beat imaging of the entire coronary tree, may be ideal for TAG320 and CO difference functional assessment of coronary arterial stenoses. Single-beat imaging on 320-detector row CT allows temporal contrast in the entire volume of the heart and eliminates step registration artefacts. These features may minimize distortions in TAG and CO difference values, which may be encountered using earlier generation 64-detector row CT. The methodology for TAG320 measurement in our study is similar to that of Choi et al. (6), who assessed TAG on 64-slice MDCT against angiographic binary stenosis. Meanwhile, the methodology for CO difference in our study was a rigorous analysis using fixed-interval ROI HU measurements extending the entire coronary tree, as has been described by Steigner et al. (8). This is in contrast to the study by Chow et al. (7), which used only ≥6 ROI HU (2 pre- and 4 post-stenoses) measurements on a 64-slice MDCT. This method, as acknowledged by the authors, is less rigorous and therefore may be inferior compared with the methodology performed in our study.

FFR as reference standard. Because TAG was previously assessed only against angiographic binary stenoses, validation of whether TAG can predict functionally significant stenosis is required and was the purpose of this study. We chose FFR as our reference standard, which is the established gold standard invasive method to assess the hemodynamic significance of coronary stenoses. We chose the value of 0.8 on FFR as the cutoff because the absence of ischemia associated with FFR >0.8 has a predictive accuracy of 95% (10).

Diagnostic accuracy of TAG320, CO differences, and CCTA for predicting significant FFR. The current study examined the diagnostic accuracy of TAG320 and CO (maximum, mean, minimum) differences in predicting functionally significant coronary stenoses. Of the CO differences, CO mean difference with a cutoff of ≥55 HU had the best diagnostic accuracy with a sensitivity of 74% and specificity of 66%. On the other hand, TAG320 with a cutoff of ≤−15.1 HU/10 mm has a sensitivity of 77% and specificity of 74%. The CO differences in proximal versus distal coronary artery opacification has been evaluated on 320-detector row CT (17). However, the diagnostic accuracy of CO differences for detecting functionally significant coronary stenoses has never been compared with TAG320. An explanation of the difference in diagnostic accuracy between TAG320 and CO differences may be that the measurement of gradients across coronary stenoses is inherently more robust than opacification differences. The gradient across a lesion is normalized for the length of lesion in question in the TAG320 methodology. However, this is not accounted for in the potentially more convenient CO differences methodology. In addition, although the CO difference methodology may offer the convenience of using 2 attenuation measurements before and after the lesion of interest, it may be more susceptible to image noise and artefacts.

The sensitivity and specificity of CCTA in our study were 94% and 66%, respectively. This is despite the high frequency of calcified lesions (69%). The diagnostic accuracy of CCTA in our study is comparable to that in the study by Meijboom et al. (3), who reported sensitivity, specificity, and diagnostic accuracy of 94%, 48%, and 64%, respectively, for CCTA in detecting FFR <0.8.

Incremental value of TAG320 to CCTA for predicting significant FFR. It is widely acknowledged that anatomic stenosis poorly predicts hemodynamic and functional significance of coronary artery stenoses, particularly in lesions with moderate stenoses (18,19). The anatomic accuracy of CCTA is further limited by suboptimal temporal resolution, spatial resolution, blooming artefact, and beam-hardening artefact from coronary calcification. The current study has demonstrated that combined functional and anatomic assessment of coronary artery stenosis is possible in a simple imaging procedure and has incremental diagnostic value in detecting functionally significant coronary arterial stenoses. As highlighted, the area under the curve to detect FFR ≤0.8 for combined TAG320 and CCTA assessment increased to 0.89 compared with TAG320 alone (0.814) or CCTA (0.79) alone (Fig. 3). The radiation dose for this combined assessment was mean 5.7 mSv in our study. This is significantly lower than CT protocols, which require additional stress perfusion imaging. The radiation dose

JACC Vol. 61, No. 12, 2013
March 26, 2013:1271–9

reported for combined CCTA and CT perfusion, which is another methodology potentially providing combined anatomic and functional significance of coronary arterial stenoses, using a 320-detector row CT ranges from 11.3 to 13.8 mSv (4,20). Furthermore, the diagnostic accuracy of TAG320 was not affected by coronary calcification, which is particularly useful because CCTA is limited in accuracy when lesions are calcified. Because previous studies have shown that functional assessment has incremental prognostic value over anatomic assessment alone (9), further studies to assess the prognostic benefit of combined TAG320 and CCTA are warranted.

Study limitations. Our results represent a retrospective single-center experience involving 54 patients and thus require confirmation with larger multicenter studies. Although TAG320 analysis has incremental value when added to CCTA, generating the linear regression coefficient between luminal attenuation and axial distance remains time-consuming. A semiautomated program allowing instantaneous TAG320 analysis would be required for this methodology to be adopted in routine clinical practice. In our study, TAG320 was computed in major epicardial vessels derived from attenuation values taken at points of the artery with a cross-sectional area >2.0 mm^2 (or diameter >1.6 mm). The value in the use of attenuation values at smaller luminal sizes or in major vessels with severe distal vessel or branch disease is not known. Therefore, we acknowledge that the application of TAG320 in smaller vessels may be a limitation. This study also excluded vessels with chronic total occlusions; thus, the applicability of TAG 320 in these vessels is not known. The TAG320 cutoff value of -15.1 in our study was retrospectively determined from receiver-operating characteristic curve analysis, which may lead to overestimation of its predictive value. In addition, the TAG320 cutoff value from our study may not be generalized for studies performed on other MDCT scanners with different scanning techniques because the value may differ. In addition, the utility of TAG320 also needs to be validated using more current acquisition and reconstruction protocols, such as the model-based iterative reconstruction algorithm ("AIDR-3D").

Conclusions

Assessment of TAG320 with a 320-detector row CT provides acceptable prediction of invasive FFR and may provide a noninvasive modality for detecting functionally significant coronary stenoses. Combined TAG320 and CCTA assessment has incremental predictive value over CCTA alone for detecting functionally significant coronary arterial stenoses. Larger studies are required to determine the diagnostic and prognostic value of combined TAG320 and CCTA assessment.

Reprint requests and correspondence: Dr. Sujith K. Seneviratne, Monash Heart, Monash Medical Centre, Cardiology, 246 Clayton Road, Clayton, Victoria 3168, Australia. E-mail: sujith.seneviratne@southernhealth.org.au.

REFERENCES

1. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 2007;244:419–28.
2. Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morello R, Valgimigli M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. J Am Coll Cardiol 2006;48:1896–910.
3. Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.
4. Ko BS, Cameron JD, Meredith IT, et al. Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. Eur Heart J 2012;33: 67–77.
5. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.
6. Choi JH, Min JK, Labounty TM, et al. Intracoronary transluminal attenuation gradient in coronary CT angiography for determining coronary artery stenosis. J Am Coll Cardiol Img 2011;4:1149–57.
7. Chow BJ, Kass M, Gagne O, et al. Can differences in corrected coronary opacification measured with computed tomography predict resting coronary artery flow? J Am Coll Cardiol 2011;57: 1280–8.
8. Steigner ML, Mitsouras D, Whitmore AG, et al. Iodinated contrast opacification gradients in normal coronary arteries imaged with prospectively ECG-gated single heart beat 320-detector row computed tomography. Circ Cardiovasc Imaging 2010;3:179–86.
9. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.
10. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol 2010;55: 173–85.
11. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
12. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
13. Robinson C, Schumacker RE. Interaction effects: centering, variance inflation factor, and interpretation issues. Multiple Linear Regression Viewpoints 2009;35:6–11.
14. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72; discussion 207–12.
15. Hausleiter J, Meyer T, Hermann F, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA 2009;301:500–7.
16. Rocha-Filho JA, Blankstein R, Shturman LD, et al. Incremental value of adenosine-induced stress myocardial perfusion imaging with dual-source CT at cardiac CT angiography. Radiology 2010; 254:410–9.
17. Rybicki FJ, Otero HJ, Steigner ML, et al. Initial evaluation of coronary images from 320-detector row computed tomography. Int J Cardiovasc Imaging 2008;24:535–46.
18. Hacker M, Jakobs T, Hack N, et al. Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary

artery stenoses in patients with stable angina. Eur J Nucl Med Mol Imaging 2007;34:4–10.
19. Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. Am J Cardiol 2007;99:450–6.
20. George RT, Arbab-Zadeh A, Miller JM, et al. Computed tomography myocardial perfusion imaging with 320-row detector computed tomography accurately detects myocardial ischemia in patients with obstructive coronary artery disease. Circ Cardiovasc Imaging 2012;5:333–40.

Key Words: coronary computed tomography angiography ▪ coronary disease ▪ fractional flow reserve ▪ ischemia ▪ transluminal attenuation gradient.